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Atty. Docket No. FAH02 P-300A

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December 29, 2004
Date

Deborah A. Witvoet
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Art Unit	:	1647
Examiner	:	Regina M. DeBerry
Applicant	:	Gregory M. Fahy, Ph.D.
Appln. No.	:	09/933,309
Filing Date	:	August 20, 2001
Confirmation No.	:	7331
For	:	GROWTH HORMONE THERAPY AND RELATED METHODS AND PHARMACEUTICAL COMPOSITIONS

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

APPELLANTS' REPLY UNDER 37 C.F.R. §1.193

This Rely Brief is in response to the Examiner's Answer dated October 29, 2004, and is primarily intended to address points of argument raised by the Examiner in the Examiner's Answer.

All of the assorted arguments and alleged bases for rejection of the claims are unreasonable, and factually and/or legally in error. Further, many of the rejections are based on requirements that are not reasonably related to any legal requirements for patentability. Appellant should not be forced to comply with arbitrary and capricious standards that do not have any legal basis. Accordingly, it is respectfully requested that the Board Of Patent

Appeals and Interferences carefully consider the inappropriateness and unreasonableness of each and every of numerous bases for rejection, and reverse each and every basis for rejection.

The Examiner's Answer states that claim 16 is indefinite because "the method comprises regenerating the patient's involuted thymus, but the steps of regenerating the involuted thymus have not been taught." This is an absurd abomination of the law. It mixes the requirements for definiteness with those of enablement. Further, the statement is factually incorrect. Appellant has disclosed in the specification several techniques for regenerating an involuted thymus and has offered evidence proving regeneration of the Appellant's own involuted thymus using one of the disclosed techniques. Specifically, the attached Declaration of Gregory M. Fahy (Appendix A), which made of record August 29, 2003, clearly demonstrates regeneration of Appellant's own thymus utilizing human growth hormone (hGH) in combination with DHEA, as described at pages 6-9 of the specification. Thus, the rejection is based on an untruthful misrepresentation of the facts, and an absurd indefiniteness rejection based on lack of enablement.

The Examiner has argued that the involuted thymus must be regenerated before the next step of injecting the immunological equivalent of the tissue or organ to be transplanted. This statement is totally irrelevant to any issues under consideration. The claims expressly require restoration of an involuted thymus and injection of material into the regenerated thymus.

The Examiner has argued that claim 16 does not set forth any steps involved in the method/process of regenerating an involuted thymus. This statement is totally irrelevant to patentability of the claims at issue. There is not any basis for forcing an Applicant to claim an invention more narrowly than is necessary to meet the statutory requirements. Having otherwise met the requirements for patentability, including novelty, nonobviousness and enablement, there is not a further requirement that Appellant include additional limitations. The invention is not directed to the specifically disclosed techniques for regenerating the thymus, but is instead directed to a tissue and organ transplanting technique involving restoration of immune system function by regenerating a patient's involuted thymus, inducing tolerance for the subsequently transplanted tissue or organ by injecting the immunological

equivalent of the tissue or organ into the patient's regenerated thymus, and then finally transplanting the organ or grafting the tissue in a conventional manner.

The Examiner has further argued that the claim does not set forth any steps involved in the method/process of regenerating an involuted thymus. This statement is factually incorrect and totally irrelevant to patentability of the claimed invention. The claim is not directed to a method or process for regenerating an involuted thymus, but is instead directed a method for transplanting organs and grafting tissues, in which one of the steps involves thymus regeneration. There is not any requirement that every step in a method claim include further steps. If this were the case, it would become exponentially more difficult to draft, interpret, and enforce patent claims. Regardless, there is not any legal basis for requiring that a claim which otherwise meets the requirements of patentability must include steps within steps.

The Examiner has argued that the claim in indefinite because "it merely recites a use without any active, positive steps delimiting how this use is actually practiced." This statement is factually incorrect, and is based on law that is inapplicable to the claims at issue. There are only two essential requirements under 35 U.S.C. §112, second paragraph. First, the claim must set forth the subject matter that the Applicant regards as the invention. There is not question that Appellant has met the first requirement of 35 U.S.C. §112, second paragraph, since there is not any evidence to the contrary, nor has the Examiner suggested that this requirement has not been met. The second requirement under 35 U.S.C. §112, second paragraph is that the claim must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent. The purpose of this requirement is to ensure that the scope of the claim is sufficiently clear so that the public is informed of the boundaries of what constitutes infringement. Appellant has defined his invention as a method for transplanting organs and grafting tissues into a patient by steps of restoring immune system function, injecting immunological equivalent material into the regenerated thymus to induce tolerance of the tissue or organ to be transplanted, and then transplanting the organ or grafting the tissue in a conventional manner. It is not necessary to further limit any of the steps, such as the thymus regeneration step to require that a particular technique is used for regenerating the thymus. Limiting the claims to require a specific

technique, such as administration of hGH and DHEA, would not make the claims more definite, it would only unnecessarily limit the scope of the claims and allow the public to freely practice the invention without infringing by utilizing other techniques disclosed in the specification for regenerating an involuted thymus. Because a member of the public would not have any uncertainly as to whether they are or are not employing the claimed process, i.e., whether they have regenerated the thymus and induced tolerance by injecting immunological equivalent material into the regenerated thymus before transplantation, the requirements of 35 U.S.C. §112, second paragraph have been satisfied.

Reference to a claim being indefinite when it merely recites a use without any active, positive step delimiting how the use is actually practiced does not have any bearing on the claims at issue. It is an inappropriate reference to MPEP 2173.05(q). This section of the MPEP is derived from the law of *Ex Parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986), which held that "A process for using monoclonal antibodies of claim 4 to isolate and purify human fibroblast interferon" was indefinite because it recited a use without any active, positive steps delimiting how this use is practiced. Rather than supporting a rejection under 35 U.S.C. §112, second paragraph, *Erlich* demonstrates that the rejection is inappropriate. The Board of Patent Appeals and Interferences made it clear that method claims need not recite all operating details to comply with 35 U.S.C. §112, second paragraph. It is only necessary that the claim "at least recite a positive, active step(s) so that the claim will set out and circumscribe a particular area with a reasonable degree of precision and particularity . . . and make it clear what subject matter these claims encompass . . . as well as making clear the subject matter from which others would be precluded." Thus, the requirement for a positive, active step in a process is not separate or different from the traditional requirement that the claim define the metes and bounds of the invention with particularity so that the public has fair notice of what acts would constitute infringement. The public can easily determine whether any particular transplant procedure includes thymus regeneration as a first step, followed by injection of a material into the thymus to induce tolerance of a substantially transplanted tissue or organ. Regardless, the relevant law on this point requires only <u>one</u> positive, active step. There is not any further requirement that each of the steps further include additional positive,

active steps. Claim 16 includes three positive, active steps, including: (1) restoring immune function by regenerating the thymus, (2) injecting immunologically equivalent material into the regenerated thymus, and (3) transplanting a tissue or organ. Thus, a rejection of the claim based on indefiniteness as outlined in MPEP 2173.05(q) and the *Erlich* case is in error.

The Examiner has also alleged that claim 16 is indefinite because the term "immunological equivalent" is a relative term which renders the claim indefinite. The Examiner has stated that the term "immunological equivalent" is indefinite because it "is not defined by the claim, [and] the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." The rejection is based on an incorrect statement of the facts, and on arbitrary requirements that do not have any reasonable relationship to the legal requirements for patentability. There is not any legal requirement that every word used in a claim must also be defined within the claim. The Board of Patent Appeals and Interferences will appreciate that it is extremely rare for a claim to actually define any word used within the claim. A requirement that all words used in a claim must be defined would lead to claims that are absurdly difficult to draft, interpret and enforce. Regardless, a rejection cannot be based on an arbitrary standard that does not have any reasonably relationship to any legal requirements for patentability. Further, Appellant has repeatedly explained that the term "immunological equivalent" is frequently used in the literature and has its ordinary literal meaning, i.e., that the material induces an immunological effect on the thymus that is equivalent to the effect of the tissue or organ that is to be transplanted into the patient. When considered in the context of the claimed invention, it is clear that the term refers to material that induces an immunological response that has the effect of improving tolerance for the subsequently transplanted tissue or organ, thereby reducing or eliminating an immune response to the transplanted tissue or organ that would cause rejection. Further, the specification expressly adopts the literal meaning of the term "immunological equivalent" by stating that the immunological equivalent materials are either "an appropriate sample of the tissue or organ to be transplanted later, or . . . any other donor-specific cells or antigens . . . that are the immunological equivalent of the tissue itself in stimulating deletion or anergy of the cells

otherwise responsible for later rejecting the transplanted tissue or organ" (page 15, lines 18-25). Several examples are provides in the specification to further illustrate the meaning of the term "immunological equivalent." In particular, the specification states (at page 16) that the "tissue may be an endogenously-derived sample in the case of those with autoimmune diseases . . . ; a joint biopsy to reverse autoimmune arthritis; or endogenous islets to reverse incipient diabetes . . ." It is abundantly clear to those capable of reading and understanding the specification that the term "immunological equivalent" unambiguously refers to material that induces tolerance for the transplanted tissue or organ. Thus, the claim clearly and unambiguously requires injecting, into a regenerated thymus, a material (the immunological equivalent of the tissue or organ to be transplanted) that induces tolerance for the subsequently transplanted tissue or organ, without any regard to degree. Therefore, the term "immunological equivalent" is not a relative term with respect to the claims at issue. A material either does or does not induce tolerance for a subsequently transplanted tissue or organ after being injected into a regenerated thymus. Clearly, the term "immunological equivalent" is not a relative term within the context of the claim. Even if there are degrees of induced tolerance for a transplanted material, the term is not a relative term because it is intended to encompass any tolerance that is induced by injecting such material into a regenerated thymus. Does the mere fact that not all structural members perform identically, i.e., provide the same degree of stability and strength, make the requirement for a "structural element" in a claim for a mechanical apparatus indefinite as a relative term? Of course not! Similarly, regardless of whether some immunological equivalent materials work faster or better than other immunological equivalent materials does not have any bearing on whether or not the material induces tolerance, just as a structural member capable of bearing a two ton load is as much a structural member as another structural member capable of bearing a one ton load.

All bases for rejection of the claims under 35 U.S.C. §112, second paragraph rely on misrepresentation of the facts, misunderstandings and/or inappropriate application of the law. Accordingly, while the bases for rejection are numerous, they are all clearly inappropriate, such that the reversal is required.

The Examiner has argued that while the literature "teaches regeneration of age-involuted thymus, the experiments were only executed in rats, there was no significant improvement of cellular immune function and there were harmful side effects (reduced testosterone concentrations, hepatic tumors)." This rejection is based on a denial of the existence of facts that are on the record, and on inappropriate generalizations based on isolated statements in the published literature.

The Examiner believed that there is some ambiguity or uncertainty in the literature as to whether immune function can be restored by thymus regeneration, and that there may be some harmful side effects associated with thymus regeneration.

The possibility of undesirable side effects associated with practice of the claimed method is not relevant to patentability. There is not any requirement that a medical procedure must be free of any and all undesirable side effects to be patentable. As will be appreciated by the Board or Patent Appeals and Interferences, there is scarcely any worthwhile human endeavor that is completely free of any and all risk of undesirable side effects. To the contrary, it is a matter of common knowledge that almost all medical procedures have some risk associated with their practice. Perfection is not a requirement of patentability, and the existence of undesirable side effects alone is not relevant to patentability of the claimed invention.

The Examiner's claim that there it not any evidence of record showing thymus regeneration other than in rats is a misrepresentation of the record. Appellant has repeatedly reminded the Examiner that Appellant has regenerated his own thymus. Appellant is not a rat! Further, the literature shows thymus regeneration for dogs and mice, and suggests thymus regeneration for humans.

The Examiner's suggestion that there is some uncertainty as to whether regeneration of the thymus will improve immune function is based on a misinterpretation of a quotation of the Goff et al. reference. There is not any evidence of record suggesting that immune function does not improve when the thymus is regenerated. Goff et al found that they could restore immunological function by using growth hormone for a time too brief to regenerate the thymus of aged dogs. This observation is not relevant to the claimed invention because it does not

include thymic regeneration. The Goff et al. reference does not provide any evidence that immunological function is not restored when thymic regeneration is achieved. Therefore, the statements of the Goff et al. reference cannot be extrapolated to cast any doubt on the claimed invention. To the contrary, what the Goff et al. reference suggests is that thymus regeneration may not be necessary in order to restore immune function. As stated in the abstract of the Goff et al. reference, "Plasma thymulin concentration increased in EVERY bGH-treated dog" (emphasis added), including both dogs whose thymuses were regenerated (the middle-aged dogs) and dogs whose thymuses did not regenerate within the one month period of study (the advanced-aged dogs)." Thus, when the quoted passage ("a change (or lack of change) in thymic morphology does not prove increased or decreased thymic function: immunological or endocrine function must also be assessed") is considered in its proper context (i.e., the entire disclosure of Goff et al.), it is apparent that Goff et al. are showing that growth hormone therapy can improve immune function without necessarily causing thymus growth, at least with the advanced-age dogs. Further, with respect to the middle-aged dogs, the Goff et al. reference teaches that growth hormone therapy induces thymus regeneration and improved immune function. There simply is nothing on record that would indicate that improved immune function is not natural consequence of thymus regeneration. Goff et al. actually proves that growth hormone therapy regenerates the thymus and improves immune function. The fact that an isolated statement in the Goff et al. reference can be misinterpreted in a manner inconsistent with the remainder of the disclosure is not relevant to patentability.

The Examiner has argued that the specification is not enabling because it "does not provide guidelines to determine thymic atrophy or involution." This is irrelevant. Techniques for determining thymic atrophy and/or involution are well known in the art, and may be omitted from the specification.

The Examiner has stated that the "specification fails to teach how a thymus can be regenerated upon administration of human growth hormone and DHEA or human growth hormone and chromium picolinate in a patient." This is a misrepresentation of the facts of record. The Examiner has been repeatedly reminded that the specification expressly discloses appropriate doses and treatment regimens for regenerating a thymus using a combination of

human growth hormone and DHEA or human growth hormone and chromium picolinate (page 6, lines 4-12 provides enablement for the combination of human growth hormone and DHEA, and page 17, lines 8-9 disclose appropriate doses for chromium picolinate are based on the insulin-lowering response attained in a particular patient). Further, Appellant has presented evidence showing regeneration of his own thymus using a combination of human growth hormone and DHEA (see the attached declaration).

The Examiner has argued that the disclosure does not provide immunological or endocrine assays or employ experiments such as magnetic resonance imaging or morphology studies, which would discern that a thymus has been regenerated. This is irrelevant. Appellant is not claiming immunological or endocrine assays, magnetic resonance imaging techniques or morphology studies. To the extend that such assays, experiments, imaging and studies may be employed in conjunction with the practice of the invention, such techniques are well known and need not be expressly disclosed, and are preferably omitted from the specification.

The Examiner has argued that the specification provides no guidance or working examples for intrathymic injection. This statement is not relevant to patentability of the claimed invention. Appellant has not claimed to have invented any new or improved intrathymic injection technique. To the contrary, it has been admitted repeatedly throughout the prosecution that such techniques are well known to those having ordinary skill in the art, and need not be described in the specification.

The Examiner has argued that the specification fails to teach or disclose working examples for transplanting an organ or grafting of tissue. This statement is irrelevant to patentability of the claimed invention. Appellant is not claiming to have invented an improved method of transplanting an organ or grafting tissue. Such techniques are routinely employed by those having ordinary skill in the art, and need not be described in the specification.

The Examiner has argued that the specification does not address "factors such as rejection, age-related thymic involution versus other types of thymic involution, the side effects of immunosuppressants, ALS versus CsA, the high incidence of tumors and other side effects associated with GH." This argument is irrelevant to patentability of the claimed invention.

The claims do not require a distinction between age-related thymic involution and other types of thymic involution, and do not require the use of immonsuppressants. Further, whether or not there is a risk of adverse side effects associated with practice of the invention is not relevant to patentability. There is not any requirement that a method must be perfect and free of any side effects in order to be patentable.

The Examiner has made an additional misrepresentation of fact by stating that the term "immunological equivalent of tissue or organ to be transplanted is not defined and the specification does not teach how to make such." The specification expressly states (page 15, lines 18-26) that appropriate tolerance-inducing materials to be injected into the regenerated thymus are "an appropriate sample of the tissue or organ to be transplanted later, or . . . any other donor-specific cells or antigens . . . that are the immunological equivalent of the tissue itself in stimulating deletion or anergy of the cells otherwise responsible for later rejecting the transplanted tissue or organ." Specific examples are listed at page 16, lines 1-9.

The Examiner has stated that neither the specification nor the literature of record teach enablement of the instant invention. This is clearly inconsistent with the record. The step of regenerating the thymus has been demonstrated by regeneration of Appellant's own thymus using human growth hormone and DHEA (see the attached declaration of record). The remaining steps of injecting cells or antibodies into the thymus, and conventional grafting of tissue or transplanting of organs are known.

The Examiner has stated that the experimentation required to practice the claimed invention would be undue for one skilled in the art at the time the invention was made for "reasons discussed above" (i.e., in the first seven and a half pages of the Examiner's Answer). Appellant is not able to address this argument because the Examiner has not provided any reasons why undue experimentation would be required.

The Examiner has argued that "due to the large quantity of experimentation necessary to regenerate an involuted thymus, administer an intrathymic injection and transplant an organ or tissue, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the state of the prior art which establishes the unpredictability of intrathymic injections and

organ/graft transplants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope." Intrathymic injection techniques and organ/tissue transplant techniques are known and do not require undue experimentation. Appellant has proven that the human thymus can be regenerated by administration of human growth hormone and DHEA. Thus, only the ordinary and routine testing and precautions associated with conventional intrathymic injection and organ transplant or tissue grafting is required to practice the invention in view of Appellant's disclosure. Routine testing and precautions do not constitute undue experimentation. There is not any evidence of record supporting the Examiner's statement that intrathymic injections are unpredictable. The unpredictability of organ/graft transplants is not relevant to patentability of the claims, since any such unpredictability does not involve undue experimentation.

The Examiner has argued that the claims fail to interrelate essential elements of the invention as defined by the Applicant in the specification, and may be rejected under 35 U.S.C. §112, second paragraph in accordance with MPEP Section 2172.01. MPEP Section 2172.01 does not apply to the claims at issue. This section of the MPEP, which is based on *In Re Mayhew*, 527 F.2d 1229 188 USPQ 356 (CCPA 1976), requires that the claims include subject matter disclosed in the specification to be essential to the invention. The Examiner has alleged that the "omitted steps of regenerating an involuted thymus are essential to the method of claim 16." Appellant is forced to speculate on the Examiner's meaning. All of the claims require a step of "restoring immune system function by regenerating the patient's involuted thymus." Thus, we believe that the Examiner is taking the position that the specific techniques for regenerating an involuted thymus disclosed in the specification (e.g., administering a combination of human growth hormone and DHEA) are essential to the claimed method. Assuming that this is what the Examiner meant, the basis for the rejection is completely inappropriate because the specification does not include any statement, and there are not any statements of record, that would suggest that any particular technique for regenerating the thymus is essential. To the contrary, Appellant has in the specification and repeatedly throughout the prosecution made it abundantly clear that other techniques may be utilized. In

particular, see page 17, line 1 through page 18, line 4, which discloses alternative methods for regenerating the thymus.

With reference to MPEP Section 2172.01, the Examiner has stated that "claim 16 does not recite active, positive steps, which delimit how a patient's involuted thymus is regenerated." The recitation of active, positive steps delimit how an invention is practice is not relevant to the law discussed under MPEP Section 2172.01. Further, the appropriate law relating to the requirement for a recitation of at least one active, positive step which delimits how a claimed method is practiced only requires that the claim (not each step of the claim) include at least one active, positive step. Claim 16, as previously discussed, includes three active, positive steps: regenerating the thymus, injecting material into the thymus to induce tolerance; and transplanting organs or tissue.

After reciting the relevant passages of the specification which define the meaning of the term "immunological equivalent," the Examiner stated that "there is not unambiguous definition of what the term does and does not encompass." There is not any explanation as to how the disclosure is ambiguous. Those having ordinary skill in the art would understand that "immunological equivalent" materials are materials that stimulate an immunological response that is equivalent to the organ that is being transplanted or tissue that is being grafted, whereby tolerance of the transplanted tissue or organ is induced. It can be determined with absolute certainty whether any such material does or does not induce an immune response that is equivalent to the organ to be transplanted and/or the tissue to be grafted. Thus, the term "immunological equivalent" is not a term of degree within the context of the claims, and the claims comply with the definiteness requirements of 35 U.S.C. §112, second paragraph.

The Examiner has alleged that any confusion on the Examiner's part between the requirements for definiteness and enablement can be attributed to form paragraph 7.34.01 which the Examiner claims that she used in making the rejection. This is a misrepresentation of the facts. Form paragraph 7.34.01 does not include any implication relating to the teachings of the specification, and does not include the words "the steps of regenerating the involuted thymus have not been taught," or any similar words. The teachings of the specification are not relevant to the definiteness requirement.

The Examiner has also argued that the claims are indefinite because the step of injecting the immunological equivalent into the thymus cannot take place until after the involuted thymus is regenerated, and because the claims fail to interrelate these essential elements. The Examiner claims that support for the rejection can be found under MPEP 2172.01. Appellant agrees that regeneration of the involuted thymus is essential to the invention, and must occur before the next step of injecting the immunological equivalent material into the thymus. However, there is not any issue with respect to the requirements stated in MPEP 2172.01, since claim 16 expressly requires regeneration of the involuted thymus before injecting the immunological equivalent into the regenerated thymus.

In response to Appellant's argument that the claims are definite because the public can determine the boundaries of which constitutes infringement, the Examiner has stated that the "instant rejection is not based on infringement." While the Examiner does not appreciate that the appropriate test for definiteness is whether the public can determine the boundaries of which constitutes infringement (MPEP 2173), it is believed that the Board of the Patent Appeals and Interferences can and will appreciate that the claims meet the definiteness requirement because the scope of the claims clearly informs the public of the boundaries of what constitutes infringement.

The Examiner has stated that claim 16 omits matter disclosed to be essential to the invention as described in the specification. There is not any indication as to what disclosed matter is essential. It is believed that the Examiner may be referring to the previously alleged essential matter of regenerating the thymus before injecting the immunological equivalent into the regenerated thymus. However, as stated above, claim 16 expressly requires regeneration before injecting the material into the thymus, since the material is injected into "the regenerated thymus."

The Examiner has stated that the claim "depends on a recited property." It is not clear what property is being referred to, where the property is recited, and/or whether such recitation and/or dependency is in any way relevant to patentability. Accordingly, Appellant is justifiably unable to respond to this new rejection and/or point of argument.

The Examiner has also argued that claim 16 "covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor." There is not any requirement in the patent laws that the specification must disclose more than the inventor knows. To the contrary, such requirement would make it impossible to patent anything. Clearly, the Examiner is attempting to base a 112, second paragraph rejection on "undue breadth." Breadth of a claim cannot be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). See MPEP 2173.04.

The Examiner has argued that the subject matter of claim 20 is essential to claim 16. Claim 20 lists specific agents useful for restoring immune system function by regenerating a patient's thymus. It should be noted that essential matter is determined by Applicant, not by the Examiner. The Applicant has never suggested that specific agents are essential.

The Examiner has argued that "Appellant uses the term 'immunological equivalent' in the definition of immunological equivalent, which is not helpful." Appellant disagrees. It is absolutely clear and certain that the expression "immunological equivalent of the tissue itself" refers to a material that stimulates deletion or anergy of the cells otherwise responsible for later rejecting the transplanted tissue or organ. Further, it is self evident that the claim requirement for injecting "the immunological equivalent of the tissue or organ to be transplanted into the patient" refers to material that elicits an immune response equivalent to that of the transplant/graft tissue. The public can determine with absolute certainty whether any particular process involves injecting the immunological equivalent of the transplant tissue into a regenerated thymus before transplanting the tissue, and therefore can determine with absolute certainty whether the claims are infringed by any particular process. Therefore, the claims comply with the requirements of 35 U.S.C. §112, second paragraph.

If the scope of the subject matter embraced by the claims is clear, and if Applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. §112, second paragraph. The scope of the subject matter embraced by the claims at issue is clear, and Applicants have not otherwise indicated that they intended the invention to be of a scope different from that defined

in the claims. Accordingly, the claims at issue comply with 35 U.S.C. §112, second paragraph. Thus, reversal of the rejection is appropriate.

It is stated that Appellant's definition for "immunological equivalent" is not helpful because it uses the term within the definition, and sets forth what the immunological equivalent material does, not what it is. There is not any legal basis for requiring that the claims limit the immunological equivalent to the specific examples set forth in the specification. The only question under 35 U.S.C. §112, second paragraph is whether the Applicant has claimed what he regards as the invention and whether the public can determine the metes and bounds of the invention. The public can ascertain what materials will stimulate deletion or anergy of cells otherwise responsible for rejecting a transplanted tissue or organ, and therefore can determine whether a particular activity would constitute infringement of the claims at issue.

The Examiner has argued that the claims are not enabled because the published literature discloses that thymus regeneration may cause certain undesirable side effects such as reduced testosterone concentration. This observation does not relate to patentability. Further, a transplant patient is very likely to risk a reduced testosterone concentration to save his life, i.e., the patient could expect the potential benefits to outweigh the risks. Perfection and/or absence of all disadvantages or risks is not a condition of patentability.

The Examiner has argued that the literature teaches that there is not a significant improvement of cellular immune function associated with thymic regeneration and that there is a "high incidence of hepatic tumors in growth hormone treated mice." This is a mischaracterization of the facts. The McCormick article expressly discloses that growth hormone treatment was beginning to improve immune function. The Goff et al. article also discloses that immunological function could be restored using growth hormone to regeneration the thymus of middle-aged dogs. The record when considered as a whole clearly indicates a correlation between thymic regeneration and restoration of immune function. The mere fact that immune system restoration may not have been observed in every case and that there may be some undesirable side effects associated with hormone therapy or other techniques for regenerating the thymus is not relevant to patentability.

The Examiner has argued that the harmful side effects that may occur could affect the patient's immune system function, thereby preventing the claimed method from being successful. This is mere speculation. There is not any evidence that thymus regeneration actually reduces immune function. The fact that there is some uncertainty does not diminish the fact that there is a substantial chance of success. A method does not need to be perfect, free of harmful side effects, or 100% effective to be patentable. The Examiner should not be permitted to selectively and unfairly impose arbitrary standards on Appellants that are neither mandated nor authorized by the patent laws.

The Examiner has stated that neither the specification nor the literature of record enable the invention, "since these goals (restoring immune function and regenerating a thymus) have not been accomplished." This is a mischaracterization of the facts of record. Goff states in the summary that the "results suggest that exogenous GH may be useful for restoration of some immune functions in aged individuals." McCormick (pages 23 and 24) discloses that growth hormone therapy was effective for regenerating the thymus of mice but that "the rejuvenation of the senescent cellular immune response is not achieved as quickly as the rejuvenation of the thymus gland. McCormick et al. speculate that the less rapid recovery of the immune function may be due to the time lag in the seeding of the peripheral lymphoid organs with newly matured and normal functioning thymocytes from the rejuvenated thymus or it may be that the thymus factors responsible for maintaining the vigor of the cellular immune response have not been present for a long enough period of time to restore peripheral lymphocytes to normal functional level. McCormick et al. further speculate that the "fact that previous studies have demonstrated the benefits of exogenous thymus factors to the senescent immune response [13, 14, 15, 16] would favor the latter explanation. Thus, it is fair to say that the literature demonstrates that restoration of immune function follows thymus regeneration.

It is argued that it is not enough that every aspect of the claimed invention has been enabled, "the enablement of the invention is based on the entire method steps taking place in patient." Appellant has proven that his own thymus was regenerated by administration of human growth hormone in combination with DHEA , in accordance with a technique disclosed in the specification. Injection of materials into a thymus is a routine matter. Similarly,

conventional organ transplant and tissue transplant techniques are routinely performed on patients. Thus, every aspect of the claimed invention is enabled, i.e., there is not any undue experimentation that is required to practice any of the individual aspects of the claimed method. The Examiner has not provided any rationale for why one having ordinary skill in the art would be able to practice each and every one of the steps of the claimed method, but would be unable to practice the entire method.

The Examiner has argued (page 22 of the Examiner's Answer) that Appellant has not actually practiced the claimed invention. It is well established that enablement does not require an actual reduction to practice.

The Examiner has argued that the individual steps of the invention are not predictable in a patient. The Examiner is apparently attempting to impose requirements and standards that are neither mandated nor authorized by the patent laws. There is scarcely any therapeutic procedure that is completely predictable and free of potential harmful side effects. This type of unpredictability, i.e., where the procedure may or may not be effective, and wherein the procedure may or may not be associated with harmful side effects, is not relevant to patentability.

The Examiner has argued that the attached Fahy Declaration fails to demonstrate that immune system function has been restored. However, the literature of record overwhelming suggests improved immune system function results from thymus regeneration.

It is stated that the specification fails to disclose any method for making and using the claimed method. This is untrue. The specification is devoted to providing information on how to practice the claimed invention. Intrathymic injection techniques and organ transplant or tissue grafting techniques are known such that a detailed discussion is not required for enablement. Sufficient guidance has been provided in the specification for the selection of appropriate immunological equivalent material for injection into a regenerated thymus. Finally, the specification provides a detailed discussion of appropriate techniques for regenerating a thymus, including appropriate therapeutic doses and therapeutic regimens. There is not any aspect of the claimed method that is not enabled. The Examiner has not alleged that there is any aspect of the claimed method that is not enabled. A person having

ordinary skill in the art would not have any additional difficulty, and would not need to engage in any undue experimentation, in order to inject material into a regenerated thymus as opposed to an involuted thymus. In fact, in all likelihood it would be easier to inject material into a regenerated thymus. Finally, there would not be any additional difficulty or undue experimentation associated with performing an organ transplant or tissue graft on a patient that has had the first two steps of the method performed than on an ordinary patient that has not been prepared in accordance with the claimed method.

The Examiner has stated that the claims are not enabled because "one would have to determine whether the thymus is involuted before it can be regenerated." The fact that the method is not appropriate for every patient is not relevant to patentability. Doctors are highly skilled professionals that are capable of determining whether the procedure is appropriate for any particular patient.

The Examiner has stated that the claims are not enabled because thymic atrophy or involution can occur in individuals under the age of 20 for other medical reasons other than age such as hypothyroid conditions or cancer. The fact that a doctor may determine that the procedure is appropriate for a person under the age of 20 is not relevant to patentability of the claimed invention. Appellant is not claiming a method for determining when his method is appropriate.

The Examiner has stated that the claims are not enabled because the specification "fails to provide parameters for discerning initial thymic atrophy or involution." Appellant is not claiming a method for discerning initial thymic atrophy or involution.

The Examiner has stated that the claims are not enabled because the specification "fails to teach limitations or factors to verify [thymic] regeneration." The literature clearly demonstrates that thymus regeneration is verifiable. In this regard, it can be noted that both the McCormick et al. reference and the Goff et al. reference verify thymic regeneration.

It is argued that "the fact that organ transplant and tissue grafting is known in the art for humans and thymus regeneration and intrathymic injection has been shown in rats, does not mean the entire combination is enabled in humans or any other patients." There is not any special or different technique for intrathymic injection in a human being versus a rat.

Intrathymic injection into a human is likely easier than into a rat. There is not any evidence of record suggesting that transplant and tissue grafting techniques involving undue experimentation would be needed in the practice of the claimed invention. Thymic regeneration has been demonstrated by the Applicant, and the prior art indicates that restoration of immune function is the expected consequence of thymic regeneration. Accordingly, there is not any aspect of the claimed invention that is not enabled, and there are not any obstacles that would prevent practice of all of the various aspects of the invention in combination.

The Examiner has stated that the claims are not enabled because the claimed method has "drawbacks, side effects, and complications." It is extremely common for therapeutic procedures to have drawbacks, side effects and complications. Such drawbacks, side effects and complications do not negate enablement. Perfection is not a requirement of patentability.

The Examiner has argued that the claimed invention is not enabled because "immunosuppressants are necessary for any type of organ transplant or tissue graft." The Examiner believes that this is relevant because the literature "does not conclusively demonstrate that immunosuppressive drugs do not interfere with the functional properties of the thymus." There is not any proof that immunosuppressants are necessary. In fact, one of the important features of the invention is to achieve tolerance for the transplanted tissue or organ without, or with a reduced need for immunosuppressants. Further, if one accepts the Examiner's statement that the literature "does not conclusively demonstrate that immunosuppressive drugs do not interfere with functional properties of the thymus," then one must also conclude that the literature does not conclusively demonstrate that immunosuppressive drugs do interfere with the functional properties of the thymus. Thus, the Examiner's argument may be characterized as speculation that immunosuppressants may be necessary (there is not proof that they are absolutely necessary) in the practice of the invention, and that immunosuppressants might interfere with the functional properties of the thymus, that such interference could reverse the tolerance induced by intrathymic injection of the immunological equivalent of the grafted tissue or transplanted organ, and that this possible reversal could render the method unsuccessful in some cases. The claims do not require a

100% success rate. Further, the effect of immunosuppressants is speculation that is unsupported by the evidence of record. Speculation that the claimed method may not always be successful is not a legitimate basis for rejection under 35 U.S.C. §112, first paragraph.

The Examiner has argued that the claims are not enabled because Appellant "fails to address the last sentence of the paragraph cited from McCormick et al., which states 'however, given the absence of tumors and placebo treated mice, these results do indicate that a correlation between growth hormone and hepatic tumors is likely'." McCormick et al. state that "The small size of our study population precludes a definitive finding [relating to hepatic tumors] given that the population under study is known to have a high tumor incidence." Thus, McCormick et al. admitted that they could not make a definitive finding regarding any correlation between growth hormone therapy and hepatic tumors in CBA male mice 24 months of age. The mere possibility that growth hormone therapy might induce hepatic tumors in a species of mice "known to have a high tumor incidence" does not suggest, and certainly does not prove, that growth hormone therapy will always cause tumors in other species. Further, it should be noted that while there are some risks associated with growth hormone therapy, replacement therapy with exogenous human growth hormone is indicated for all children with short stature who have a documented growth hormone deficiency. (*The Merck Manual*, 16th Edition, Merck Research Laboratories, 1992 at page 2223.) It is respectfully submitted that if growth hormone therapy is indicated for all children with short stature having documented growth hormone deficiency, then it is reasonable and appropriate to subject transplant and/or graft patients to the same risks associated with growth hormone therapy to improve organ/graft tolerance and potentially save lives.

The Examiner has stated that she "finds Appellant's statement, 'the claims are not directed to a method for transplanting organs or tissues with a guarantee that the patient will not develop tumors' disconcerting." The Examiner's finding is not relevant to patentability of the claimed invention.

The Examiner has asked (page 37 of the Examiner's Answer) Appellant to "cite where Goff et al. teach" that in old-age dog populations, immune function was improved before

thymic regeneration took place. The relevant statements of Goff et al. can be found at the middle of the second full paragraph at page 585, which states as follows:

> The present results indicate that bGH treatment did stimulate the endocrine function of the thymus, as measured by its thymulin production. As demonstrated in Figure 4, even the oldest dogs studied (which had no change in thymic morphology) had consistent increase in plasma thymulin concentrations.

At page 585, last paragraph, the Goff et al. article states as follows:

> We have demonstrated that GH treatment not only improves thymic morphology in middle aged dogs, but also thymic function as evidenced by increases in thymulin levels even in the oldest dog studied. The results suggest that exogenous GH may be useful for restoration of some immune functions in aged individuals.

Thus, rather than casting doubt on the effectiveness of the invention, the Goff et al. reference provides evidence that the claimed method would be successful.

The Examiner has stated that Appellant's statement that the Goff reference teaches that there is an increase in thymic function associated with increased thymic mass is incorrect. Appellant disagrees. The summary includes the following relevant statement:

> In middle-aged but not old-aged dogs, bGH treatment resulted in rejuvenation of thymic morphological features as determined by stereological and histomorphological procedures. The results suggest that exogenous GH may be useful for restoration of some immune functions in aged individuals.

The results referred to in the second sentence quoted above are rejuvenation of thymic morphological features. Thus, Goff et al. are stating that rejuvenation of thymic morphological features suggests that exogenous GH may be useful for restoration of some immune functions in aged individuals. Clearly, Goff et al. are implying an associated between thymic regeneration and restoration of immune function.

The Examiner has stated that it is important that the Goff et al. reference states "that in contrast to the middle-aged dogs there were not detectable histomorphological changes in the thymus of the old-aged dogs." The Examiner apparently believes that this is important because

it supports the Examiner's position that the Goff et al. reference teaches that there is not any increase in thymic function, immunological function or endocrine function associated with an increase in thymic mass. The origin of the Examiner's belief is in the statement of Goff et al. that "a change (or a lack of change) in thymic morphology does not prove increased or decreased thymic function, immunological or endocrine function must also be assessed." Contrary to the remaining teachings of the Goff et al. reference, the Examiner has taken the position that this statement means that there is not any connection between thymic regeneration and restoration of immune function. This is inconsistent with the disclosure of a relationship between thymic morphological features and restoration of immune function which is set forth in the summary of the Goff et al. reference. Goff et al. states that "in contrast to the middle-aged dogs, there was no detectable histomorphological change in the thymus glands of the old dogs, which could be interpreted as a loss of the ability to respond to bGH in advanced age," and that "the present results indicate that bGH treatment did stimulate the endocrine function of the thymus as measured by its thymulin production . . . even the oldest dog studied . . . had consistent increases in plasma thymulin concentrations." Goff et al. are suggesting that there could be an increase in thymic function even if there is not an increase in thymic mass. Granted, there is at least the slightest suggestion that there is a possibility that thymic regeneration could occur without improved immune function. However, this is not consistent with the remainder of the Goff et al. article and other relevant literature which strongly suggest that restoration of immune function is a consequence of thymic regeneration.

The Examiner has stated that Appellant has misinterpreted the teachings of Goff, which according to the Examiner "does not teach that there is definitely an increase in thymic function associated with an increase in thymic mass." The Examiner has reasoned that if this were the case, "the old-aged dogs would have histomorphological changes in the thymus." In essence, the Examiner's reasoning is that Goff et al. do not teach that thymic function increases as a result of an increase in thymic mass because the results show an increase in thymic function without an associated increase in thymic mass. While these results would suggest that an increase in thymic function can occur without an associated increase in thymic mass, it does not create any inference with respect to whether an increase in thymic mass will

necessarily cause in increase in thymic function. Further, it is absolutely clear from the passages quoted above from the summary and conclusion that Goff et al. appreciate that an increase in thymic function is associated with an increase in thymic mass. This fact is not negated by evidence showing an increase in thymic mass is not always necessary to achieve an increase in thymic function.

The Examiner has stated that the claimed method in not enabled because Goff et al. discloses "that stresses, viral infections, and other hormones in addition to growth hormone can affect thymus morphology." The possibility that stresses, viral infections and other hormones could influence success of the claimed method is not relevant to patentability. As with all other therapeutic procedures, it is expected that the medical practitioner would take into consideration and attempt to minimize the influence of stresses, viral infections, other hormones, etc. Appellant is not claiming that the method can be practiced without consideration of such influences. Accordingly such influences are not relevant to patentability.

The Examiner has taken the position that the claims are not enabled because "the administration of human growth hormone (HGH) is known to decrease the body's responsiveness to insulin." The specification expressly discloses working examples that show that co-administration of DHEA prevents an increase in insulation levels normally associated with HGH therapy. This is shown in Experiments 1 and 2. Thus, Appellant has demonstrated that co-administration of DHEA prevents the increased insulin levels normally associated with HGH therapy. Therefore, the claimed method is enabled with respect to a procedure that does not cause unacceptable increase in insulin level.

The Examiner has stated that Appellant's statement that co-administration of DHEA prevents the increase of insulation levels normally associated with HGH therapy is incorrect. Appellant disagrees. Experiment 1 shows that DHEA can be used to prevent insulin rise associated with release of HGH upon administration of arginine; and Experiment 2 shows that DHEA can be co-administered to prevent insulin increase during administration of human growth hormone (HGH).

The Examiner has argued that the claims are not enabled because "the specification does not teach the administration of HGH." This is incorrect. The specification repeatedly

teaches the administration of human growth hormone as a technique for regenerating the thymus.

The Examiner has stated that he claims are not enabled because "the increased likelihood of developing heart disease and hypertension are factors to be considered." While such factors should be considered by a practitioner practicing the claimed invention, such considerations do not negate patentability of the invention. It is always necessary to take into consideration various factors such as risks associated with the developing heart disease or hypertension. However, patient evaluation and other considerations are routine, and do not involve undue experimentation. Accordingly, the existences of such considerations are not relevant to the enablement requirement.

The Examiner has stated that the claims are not enabled because the Fahy Declaration "only teaches the co-administration of DHEA and HGH," and "fails to teach intrathymic injection and organ transplant/tissue graft." Intrathymic injection of materials, as admitted by the Examiner, is well known, at least with respect to laboratory animals. There is not any reason to believe that skilled physicians would have greater difficulty injecting materials into a thymus than a laboratory technician would. While Dr. Fahy was willing and eager to demonstrate thymic regeneration, it is completely unnecessary that Dr. Fahy should have the other steps of intrathymic injection and transplant performed on his body, as these techniques are well known in the art.

The Examiner has stated that the claims are not enabled because "the claims are not limited to the treatment of humans." The Examiner believes that the expression "patient" in the claim and the fact that the specification does not disclose treatment of non-human animals implies that the claims are limited to humans. The word "patient" means "one under medical treatment." Thus, use of the word "patient" in the claim does not infer that the claim is limited to the treatment of humans. Similarly, the examples from the specification cannot be read into the claim. Thus, the claims encompass both the treatment of human and animal patients. Further, the claims are enabled with respect to the treatment of humans, since one having ordinary skill in the art could easily adapt known techniques for intrathymic injection in animals to human patients. The Examiner has not provided any explanation as to why one

having ordinary skill in the art could not easily adapt techniques of intrathymic injection into non-human animals so that they could be used on humans.

The Examiner has concluded that "the Odorico reference is not applicable to the instant claimed method," because "the thymus in the rat was not regenerated before the intrathymic injection and the scientists used different tissue for the intrathymic injection and tissue graft." However, there is not any evidence that a regenerated thymus is functionally different from a non-atrophied thymus. The intrathymic injection of a tissue from the same donor that is different from the tissue to be later transplanted (the immunological equivalent) is extensively discussed as being encompassed by the Appellant's method. There is not any basis in fact for the Examiner's conclusion. Thus, the teaching of Odorico et al. of intrathymic injection of donor spleen cells and the concurrent administration of anti-lipocit serum before cardiac allograph in rats does provide enablement for the step of injecting the immunological equivalent of the tissue or the organ to be transplanted into the patient into the regenerated thymus.

The Examiner has concluded that that claims are not enabled because "neither the instant specification nor the Fahy Declaration teach the instant invention." The specification teaches the invention as claimed. The specification teaches that if all of its directions are followed, the objects of the invention will be obtained. The claims are enabled in every regard. Every aspect of the claimed invention is fully enabled by the specification or known.

It is respectfully submitted that the Examiner has not explained how every aspect of a claimed invention can be enabled, but the claims as a whole somehow is not enabled. In attempt to provide explanation, the Examiner claims that the literature suggests that there might be some adverse side effects associated with practice of the claimed invention, and that in some cases the claimed method may not be successful. None of these arguments support a rejection based on nonenablement.

CONCLUSION

It is respectfully submitted that the claims are definite to the extent that they include three active, positive steps, and to the extent that the term "immunological equivalent" has a self evident meaning that is also defined in the specification and which can be clearly

understood within the context of the claimed invention. Further, it is respectfully submitted that the claims are enabled to the extent that every aspect of the claimed invention is either well known in the art or enabled by the specification, and there is not any explanation provided as to how every aspect of a claimed invention can be enabled, while the claim as a whole is not enabled.

Respectfully submitted,

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By: Price, Heneveld, Cooper,
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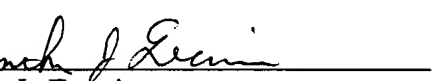
December 29, 2004
Date



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